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(54) Title: CHEMICAL PROCESSES AND INTERMEDIATES

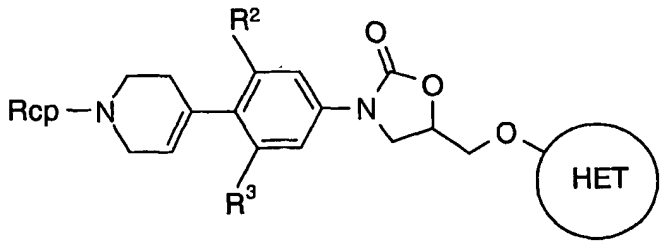
(57) Abstract: A method of coupling an alcohol group of an organic compound to a multidentate nucleophilic compound, which method comprises adding to a reaction vessel containing an activating agent, said nucleophilic compound, said alcohol and a trisubstituted phosphine or trisubsituted phosphite, wherein the trisubstituted phosphine or trisubstituted phosphite and the activating agent together form a redox system which is able to operate a Mitsunobu reaction, resulting in formation of a coupled compound.

Chemical Processes and Intermediates

The invention relates to chemical processes, and in particular to processes which involve reactions known as Mitsunobu reactions. In particular, the processes of the invention are useful in the preparation of intermediates used in the production of certain oxazolidinone anti-Gram positive bacterial agents.

The Mitsunobu reaction is a widely applicable reaction which allows the coupling of nucleophiles (NuH) to alcohols and particularly secondary alcohols. It is described for example in Progress in the Mitsunobu reaction: a Review, by D.L. Hughes in Organic Preparations and Procedures International, 28, (2) p127-164. A particular example of such as reaction is described by Nakamura et al. Tet. Lett. 31, 5, 699-702 (1990). Where the secondary alcohol is chiral, a clean inversion of the stereochemistry takes place. The reaction utilises a redox system made up of an activating agent such as an azodicarboxylate and a trisubstituted phosphine or phosphite. In these reactions, conventionally, the redox system is completed by adding the activating agent to a solution of the remaining components of the reaction mixture (i.e. the nucleophile, the alcohol and the trisubstituted phosphine.

Where the nucleophiles are multidentate, in that they contain more than one nucleophilic site, for example, both an oxygen and a nitrogen atom, it has been recognised that coupling may take place at both sites. This leads to a mixture of N- and O- linked products for instance, although generally the O-linked product is predominant. Our International Patent Application No. WO 99/64417 describes a new class of antibacterial oxazolidinone compounds which are effective as anti-Gram positive bacterial agents, and certain processes for their preparation. These include compounds of formula (I):



(I)

wherein

HET is a C-linked 5-membered heteroaryl ring containing 2 to 4 heteroatoms independently selected from N, O and S, which ring is optionally substituted on an available carbon atom by

1 or 2 substituents independently selected from (1-4C)alkyl, amino, (1-4C)alkylamino, (1-4C)alkoxy and halogen, and/or on an available nitrogen atom (provided that the ring is not thereby quaternised) by (1-4C)alkyl;

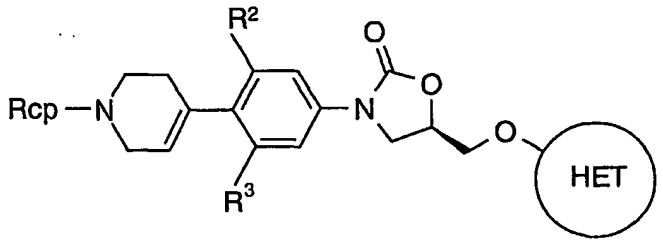
R^2 and R^3 are independently hydrogen or fluoro;

Rcp is of the formula $R^{13}CO$- (wherein R^{13} is (1-10C)alkyl substituted by two or more hydroxy groups; 2 of which are in a 1,2-diol orientation, ie. there is a terminal primary alcohol with an adjacent secondary alcohol), or pharmaceutically-acceptable salts, or in-vivo-hydrolysable esters thereof.

It is to be understood that all terms used in the definition of formula I above are as defined in WO 99/64417.

Of the above compounds, those in which HET is (unsubstituted) isoxazol-3-yl, 1,2,4-oxadiazol-3-yl, isothiazol-3-yl or 1,2,5-thiadiazol-3-yl are preferred.

Of the compounds of formula (I), those of formula (I-1) are the pharmaceutically active anti-bacterial enantiomer. The pure enantiomer depicted in (I-1), or mixtures of the 5R and 5S enantiomers, for example a racemic mixture are included in WO 99/64417. If a mixture of enantiomers is used, a larger amount (depending upon the ratio of the enantiomers) will be required to achieve the same effect as the same weight of the pharmaceutically active enantiomer. For the avoidance of doubt the enantiomer depicted below is the 5R enantiomer.



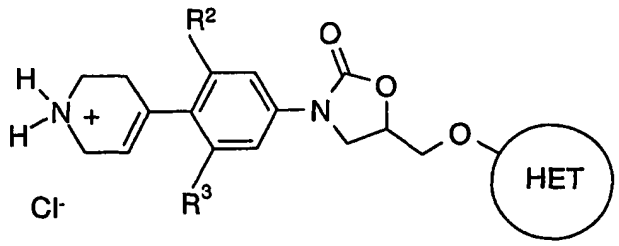
(I-1)

Furthermore, some compounds of the formula (I) and (I-1) may have other chiral centres, and such optical and diastereo-isomers, and racemic mixtures may possess antibacterial activity. It is well known in the art how to prepare optically-active forms (for example by resolution of the racemic form by recrystallisation techniques, by chiral synthesis, by enzymatic resolution, by biotransformation or by chromatographic separation) and how to determine antibacterial activity.

Of the above compounds of formula (I)7 and (I-1), 5(R)-isoxazol-3-yloxymethyl-3-(4-

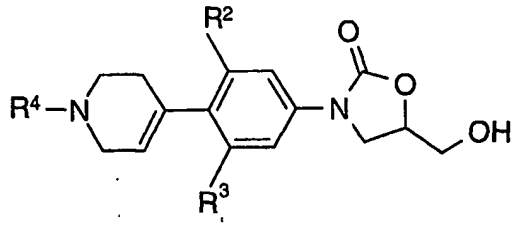
(1-(2(S)-hydroxy-3-phosphoryl-propanoyl)-1,2,5,6-tetrahydropyrid-4-yl)-3,5-difluorophenyl)oxazolidin-2-one is especially preferred.

Various methods for preparing compounds of formula (I) and (I-1) are described in WO 99/64417. One such method utilises a Mitsunobu reaction. During this reaction, compounds of formula (IIA)



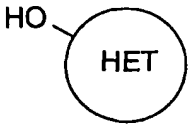
(IIA)

(where R^2, R^3 and HET are as defined in relation to formula (I)) are formed by adding diisopropylazodicarboxylate (DIAD) to a solution of a compound of formula (IIIA)



(IIIA)

(where R^2 and R^3 are as defined above, and R^4 is hydrogen or a protecting group such as benzyl or a salt HR^5 where R^5 is an anion such as halides in particular chloride); a compound of formula (IVA)



(IVA)

(where HET is as described above); and triphenylphosphine, in tetrahydrofuran; and thereafter, if necessary, removing any protecting group R^4. Removal of protecting groups R^4 are carried out using conventional methods. In particular, Reference Example 6 of WO 99/64417 describes the removal of a benzyl protecting group R^4 by reaction of a solution of the isolated compound of formula (IIA) in dichloromethane with 1-chloroethyl chloroformate.

By-products of this reaction are compounds where the HET ring is inappropriately bound in the compound of formula (IIA). For example where HET is a 5-isoxazole ring, as in

the preferred compounds, it has been found that an impurity is a result of N-linkage.

The applicants have surprisingly found that by altering the way in which the reagents used in a Mitsunobu reaction using a multidentate nucleophile are added together, improvements in the reaction and less by-products result.

According to the present invention there is provided a method of coupling an alcohol group of an organic compound to a multidentate nucleophilic compound, which method comprises adding to a reaction vessel containing an activating agent, said nucleophilic compound, said alcohol and a trisubstituted phosphine or trisubsituted phosphite, wherein the trisubstituted phosphine or trisubstituted phosphite and the activating agent together form a redox system which is able to operate a Mitsunobu reaction, resulting in formation of a coupled compound.

Suitable redox sytems are known in the art and are described for example in the review by D.L. Hughes et al (supra.) and "The Mitsunobu Reaction" by D.L. Hughes, Org. React. (N. Y.) (1992), 42 335-656. CODEN: ORREAW ISSN: 0078-6179.

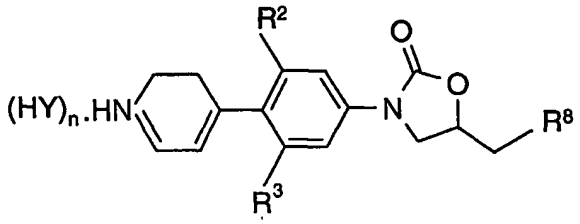
In particular, the activating agent is an azodicarboxylate, in particular a di(1-6C)alkylazodicarboxylate (such as DIAD as mentioned above, and diethylazodicarboxylate (DEAD)) or a diheterocyclic system (such as 1,1'-(azodicarbonyl)dipiperidine) or a tetra alkyl azodicarboxylate such as N,N, N'N'-tetramethyl-azodicarboxylate or N,N,N',N'tetraisopropylazodicarboxylates.

Suitable substituents for the phosphine and phosphite groups are optionally substituted aryl, alkyl, or aralkyl groups. Suitable optional substitutents for such groups are an amino, or mono- or dialkyl amino groups such as dimethyl amino. Particular examples are triphenylphosphine, tributylphosphine, methyldiphenylphosphine, dimethylaminophenyldiphenyl phosphine and triethylphosphite. A preferred example however is triphenylphosphine.

As used herein, the term "alkyl" refers to straight or branched alkyl chains suitably containing from 1 to 10 and preferably from 1 to 6 carbon atoms. The term "aryl" includes phenyl and napthyl. The term "aralkyl" refers to alkyl groups substituted with aryl groups, such as benzyl. The term "heterocyclic" refers to rings of up to 10 and preferably up to 7 atoms which include one or more heteroatoms selected from oxygen, nitrogen or sulphur. The rings may be saturated or unsaturated, but are preferably saturated rings such as piperidine rings.

The alcohol used in the reaction may be any compound of the desired structure. Where these contain nucleophilic groups, these may be protected using conventional methods. Similarly, the multidentate ligand may be of any desired structure, depending upon the nature of the final product required. These may be chemical products such as pharmaceuticals, or intermediates to chemical products.

In a particular embodiment, the invention provides a process for preparing a compound of formula (II) or a hydrate salt thereof,



(II)

wherein n is 0 or 1, Y is an anion;

R^8 is $-OR^9$, $-SR^9$, $-NHR^{10}$ or $-NR^{11}R^{12}$, where

R^9 is a C-linked 5-membered heteroaryl ring containing 2 to 4 heteroatoms independently selected from N, O and S, which ring is optionally substituted on an available carbon atom by 1 or 2 substituents independently selected from (1-4C)alkyl, amino, (1-4C)alkylamino, (1-4C)alkoxy and halogen, and/or on an available nitrogen atom (provided that the ring is not thereby quaternised) by (1-4C)alkyl; or

R^9 is a C-linked 6-membered heteroaryl ring containing 1 or 2 nitrogen heteroatoms, which ring is optionally substituted on any available C atom (provided that when the N atom is adjacent to the link, there is no substitution on any C atom that is adjacent to this N atom) by 1, 2 or 3 substituents independently selected from (1-4C)alkyl, amino, (1-4C)alkylamino, (1-4C)alkoxy, (1-4C)alkoxycarbonyl and halogen;

R^{10} is is a C-linked 5-membered heteroaryl ring containing 2 to 4 heteroatoms independently selected from N, O and S, which ring is optionally substituted on an available carbon atom by 1 or 2 substituents independently selected from (1-4C)alkyl, amino, (1-4C)alkylamino, (1-4C)alkoxy, (1-4C)alkoxycarbonyl and halogen, and/or on an available nitrogen atom (provided that the ring is not thereby quaternised) by (1-4C)alkyl;

or

R^{10} is a C-linked 6-membered heteroaryl ring containing 2 or 3 nitrogen heteroatoms, which

ring is optionally substituted on any available C atom by 1, 2 or 3 substituents independently selected from (1-4C)alkyl, amino, (1-4C)alkylamino, (1-4C)alkoxy, (1-4C)alkoxycarbonyl and halogen;

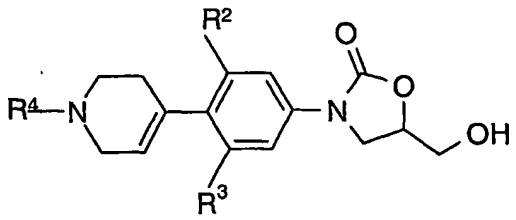
R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 5-membered heteroaryl ring, containing either (i) 1 to 3 further nitrogen heteroatoms or (ii) a further heteroatom selected from O and S together with an optional further nitrogen heteroatom; which ring is optionally substituted on a C atom by an oxo or thioxo group; and/or the ring is optionally substituted on a C atom by 1 or 2 (1-4C)alkyl groups; and/or on an available nitrogen atom (provided that the ring is not thereby quaternised) by (1-4C)alkyl; or

R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 6-membered heteroaryl ring containing up to three nitrogen heteroatoms in total (including the linking heteroatom), which ring is substituted on a suitable C atom by oxo or thioxo and optionally substituted on any available C atom by 1 or 2 (1-4C)alkyl substituents;

R^2 and R^3 are independently hydrogen or fluoro;

which process comprises adding to a reaction vessel containing an activating agent

(i) a compound of formula (III)



(III)

where R^2 and R^3 are as defined above, and R^4 is hydrogen or a protecting group such as benzyl,

(ii) a compound of formula (IV)

$$XR^8$$

(IV)

where R^8 is as described above, and

(iii) a trisubstituted phosphine or phosphite,

and thereafter, if necessary or desired carrying out one or more of the following steps:

a) removing any protecting group R^4;

b) recrystallising the product from water or a mixture of water in admixture with another solvent.

Compounds of formula (II) are useful intermediates for the production of certain oxazolidinone anti-Gram positive bacterial agents such as those described in WO 99/64417.

The applicants have found that by conducting the reaction in a different order from that usually employed in such Mitsunobu coupling reactions, i.e. by inverse addition of the substrates to the coupling reagent as described herein, a more controlled reaction occurs and the product contains less isomeric by-products. The enhancement in ratio can be significantly greater, for example in the order of 50:1 of the desired isomer:unwanted isomer.

Suitably reagents (i), (ii) and (iii) above are premixed and added together to a solution of the activating agent.

The reaction between the compound of formula (III) and (IV) is suitably effected in an organic solvent such as tetrahydrofuran. Low temperatures, for example from –20 to 20°C, preferably from –5 to 0°C and most preferably from –5 to -2°C are suitably employed.

Preferably the amount of activating agent such as diisopropylazodicarboxylate used in the process is greater than the stoichiometric amount required. Preferably is at least 1.4equivalents of activating agent is used for every one equivalent of the alcohol, which in this case is of formula (III).

Suitably also, an excess of the phosphine or phosphite such as triphenylphosphine is included in the reaction mixture, for example at least 1.55equivalents to the amount of alcohol, such as the alcohol of formula (III).

Preferred compounds of formula (II) are as described in WO 99/64417.

Suitably, in the compound of formula (II), $-R^8$ is $-OR^9$.

Examples of compounds of formula (II) where R^8 is a group $-NR^{11}R^{12}$, and methods for preparing them, are described in copending International Patent Application no. PCT/GB01/01815. Particular examples of group R^8 in this case is N-linked tetrazole or triazole.

Examples of compounds of formula (II) where R^8 is a group $-NHR^{10}$ and methods of preparation are shown in WO00/21960. Particular examples of R^{10} are isoxazol-3-yl, isoxazol-5-yl, 1,2,4-oxadiazol-3-yl, isothiazol-3-yl, 1,2,4-thiadiazol-3-yl or 1,2,5-thiadiazol-3-yl.

In addition, it may be preferred that in the compound of formula (II), R^9 is a C-linked 5-membered heteroaryl ring containing 2 to 4 heteroatoms independently selected from N, O and S, which ring is optionally substituted on an available carbon atom by 1 or 2 substituents

independently selected from (1-4C)alkyl, amino, (1-4C)alkylamino, (1-4C)alkoxy and halogen, and/or on an available nitrogen atom (provided that the ring is not thereby quaternised) by (1-4C)alkyl.

Preferably, R^8 is a group OR^9. A particular example of a group R^9 is an isoxazole group, and particularly a isoxazol-3-yl.

A particular example of a compound of formula (IV) is 3-hydroxyisoxazole. This compound is suitably added to the reaction mixture in the form of a solution in an organic solvent such as butyronitrile.

Suitably R^2 and R^3 are fluorine.

Suitably R^4 is a protecting group such as benzyl.

Removal of any group R^4 is suitably effected directly, in situ, using conventional methods. For example, a benzyl protecting group may be removed by formation of an intermediate carbamate using diisopropylethylamine (DIPEA) and 1-chloroethylchloroformate, and subsequently acidifying the carbamate using a mineral acid such as hydrochloric acid.

The nature of the acid used may affect the nature of the anion Y in formula (I). In particular, Y will be a halide such as chloride, fluoride, bromide or iodide, but may be other salt forms such as sulphates, acetates such as trifluoroacetate, depending upon the particular acid used. Alternatively, the nature of the anion Y may be changed after production to other anions, using conventional methods.

Recrystallisation of the product from non-aqueous organic solvents or solvent mixtures has been found to give only a small or negligable purification in terms of the isomer ratio enhancement. However, the applicants have surprisingly found that recrystallisation from water or from solvent/water mixtures (step b) so as to crystallise the product as a hydrate, gives unexpectedly high differentiation between isomers. This is believed to be due to significantly different crystal packing between isomers, when present as their hydrates. The resultant hydrate salt can then be used in the subsequent processing to produce a compound of formula (II).

Suitable solvents for use in the solvent/water mixtures include water miscible or immiscible solvents. Examples include acetone, ethyl acetate or alcohols, such as alkyl alcohols including butanol, methanol, ethanol or mixtures such as Industrial Methylated Spirit 74 op (IMS).

Hydrates of compounds of formula (II) are novel and so form a further aspect of the invention. It is to be understood that the invention encompasses both stoichiometric and non-stoichiometric hydrates. Preferably the water of hydration content of the hydrate is approximately 1 – 5% w/w. More preferably the water of hydration content is approximately 4% w/w. A particularly preferred hydrate of a compound of formula (II) is a hydrated form of 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1,2,5,6-tetrahydropyrid-4-yl-3,5-difluorophenyl)oxazolidin-2-one, preferably when the water of hydration content of the hydrate is 4% w/w.

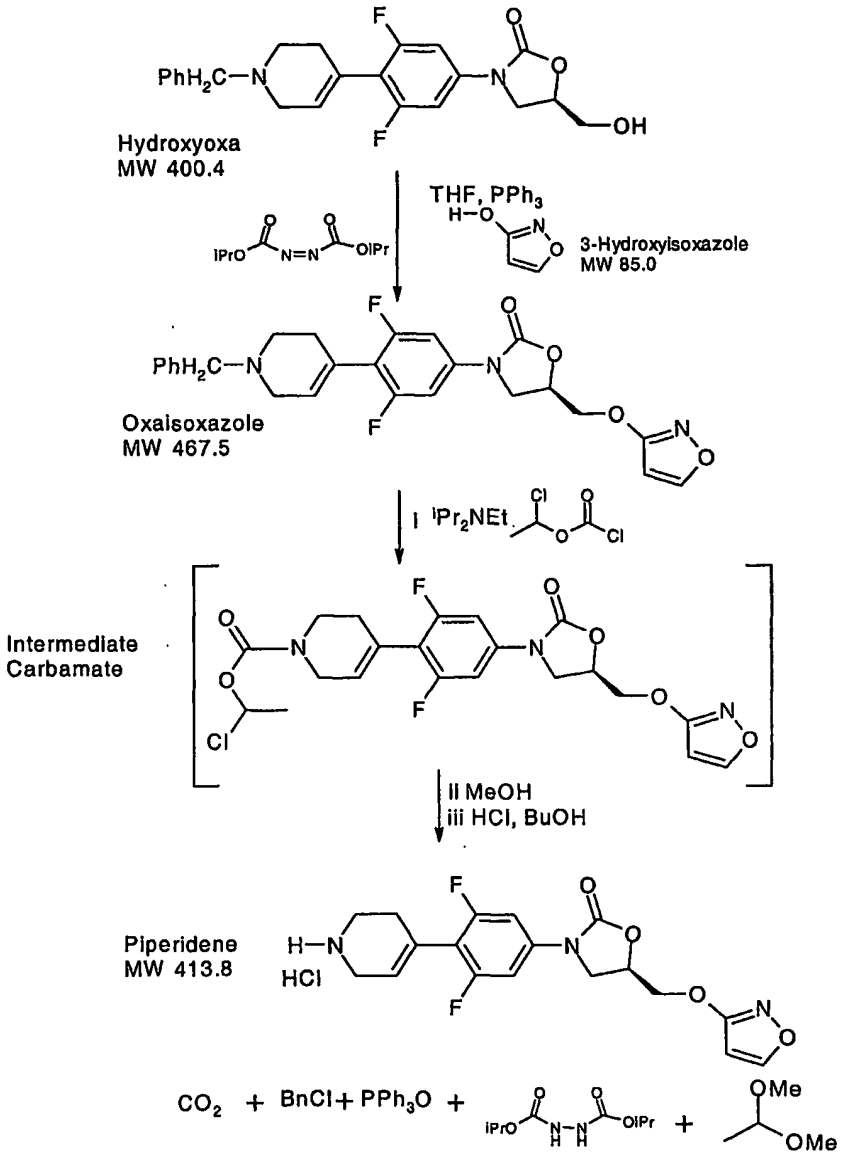
A further aspect of the invention comprises a process for purifying a compound of formula (II) as defined above, said method comprising dissolving the compound in water or water in admixture with a further solvent, and allowing the hydrate salt to crystallise therefrom. Suitable further solvents are those described above in relation to the water/solvent mixtures.

Compounds of formula (III) and (IV) are either known compounds or they may be prepared from known compounds by conventional methods.

The invention will now be illustrated but not limited by reference to the following Examples.

Example 1

Preparation of 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1,2,5,6-tetrahydropyrid-4-yl-3,5-difluorophenyl)oxazolidin-2-one



Diisopropyl azodicarboxylate (DIAD) (49.7ml) was added to tetrahydrofuran (200ml) contained in a first reaction vessel. The stirred contents of the vessel were cooled to -5°C.

5(R)-Hydroxymethyl-3-(4-(1-benxyl-1,2,5,6-tetrahydropyrid-4-yl-3,5-difluorophenyl)oxazolindin-2-one (Hydroxyoxa in the above scheme) (70g) was added to a second vessel under an inert nitrogen atmosphere. Triphenylphosphine (71.8g) and

tetrahydrofuran (450ml) were added to the second vessel and the contents warmed to give a clear solution. The vessel was then cooled to <30°C and a solution of 3-hydroxyisoxazole in butyronitrile (194.2g, 8.04%w/w, 1.05mol eq, prepared as described below) added in a single portion.

The contents of the second vessel were then transferred to the first vessel via a jacketed dropping funnel maintained at a temperature of 25-28°C over a period of 3 hours. The product is a solution of the oxaisoxazole in the above scheme.

Diisopropylethylamine (DIPEA) (15.4ml) followed by 1-chloroethylchloroformate (ACE-Cl) (31.9ml) were charged to the chilled (0-2°C) oxaisoxazole solution and the reaction mixture was warmed to room temperature. Methanol (14.1ml) was added and the reaction is heated to 60°C and held at this temperature for 30 minutes. The warm reaction mixture is transferred to a solution of n-butanol (350ml) and hydrochloric acid (18ml). The reaction mass was concentrated by reduced pressure distillation to induce crystallisation. After cooling the desired product was filtered, washed and oven dried (42.15 g (60.8%).

Preparation of 3-hydroxyisoxazole

Hydroxylamine hydrochloride (59.4g) was dissolved in water (360ml) at -5°C under an inert atmosphere. Sodium hydroxide (10.8N, 167 ml, 2.1 mol eq) was added to the solution via a pressure equalised funnel, maintaining the temperature below -3°C. Water (45ml) is added through the funnel and the resulting clear solution warmed to 12°C over 15 minutes.

A solution of ethyl propiolate (79.7g, 0.95 mol eq) in tetrahydrofuran (THF) (120ml) is added to the first solution at a uniform rate, maintaining the temperature of the first solution below 15°C.

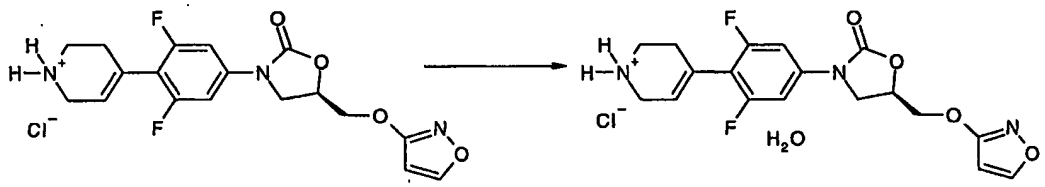
The solution is warmed to 20°C over 15 minutes. THF (30ml) is added, the solution warmed to 55°C and maintained at this temperature for 3 hours, then cooled to 20°C over 1 hour and may be held at this temperature for up to 16 hours.

The solution is cooled to -5°C before addition of concentrated hydrochloric acid (90ml) through a pressure equalised funnel, maintaining the temperature below 3°C. The resulting mixture has a pH of 0.5. Water (10ml) is added through the funnel and the mixture warmed to 20°C. THF (90ml) and butyronitrile (300ml) are added and the mixture agitated for 10 minutes. The aqueous layer is separated, washed with butyronitrile (300ml) and the combined organic layers washed with 2M hydrochloric acid (400ml) (10 minute agitation of the mixture). The organic layer is diluted with butyronitrile (600ml) and the solution

concentrated by reduced pressure distillation at 60°C until the volume is equal to that of the reaction mixture prior to addition of THF/butyronitrile. Addition of butyronitrile and distillation may be repeated such that same final volume is obtained and the water content of the solution is 0.05-0.07% w/w maximum. The strength of the resulting hydroxyisoxazole solution is calculated to ensure correct addition to the process described above; the solution strength is typically approximately 8% w/w.

Example 2

Recrystallisation of 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1,2,5,6-tetrahydropyrid-4-yl-3,5-difluorophenyl)oxazolidin-2-one



The title compound, prepared as described in Example 1 (100g) was added to water (200ml) and warmed to 80°C with stirring to form a solution. The contents were held at 80°C for 10 minutes and then filtered hot. The solution was cooled to allow the product crystallise. The desired product in the form of the hydrate salt was isolated by filtration, washed with water and dried. (78.1g, 83.1% yield).

Claims

1. A method of coupling an alcohol group of an organic compound to a multidentate nucleophilic compound, which method comprises adding to a reaction vessel containing an activating agent, said nucleophilic compound, said alcohol and a trisubstituted phosphine or trisubsituted phosphite, wherein the trisubstituted phosphine or trisubstituted phosphite and the activating agent together form a redox system which is able to operate a Mitsunobu reaction, resulting in formation of a coupled compound.

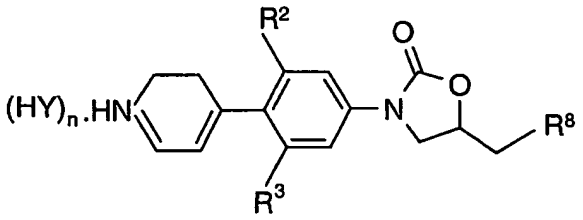
2. A method according to claim 1 wherein the activating agent is an azodicarboxylate.

3. A method according to claim 2 wherein the azodicarboxylate is a di(1-6C)alkylazodicarboxylate, a diheterocyclic system or a tetra alkyl azodicarboxylate.

4. A method according to any one of the preceding claims wherein the redox system includes a trisubstituted phosphine.

5. A method according to claim 4 wherein the trisubstituted phosphine is triphenylphosphine.

6. A process according to any one of the preceding claims for the preparation of a compound of formula (II) or a hydrate salt thereof,



(II)

wherein n is 0 or 1, Y is an anion;

R^8 is $-OR^9$, $-SR^9$, $-NHR^{10}$ or $-NR^{11}R^{12}$, where

R^9 is a C-linked 5-membered heteroaryl ring containing 2 to 4 heteroatoms independently selected from N, O and S, which ring is optionally substituted on an available carbon atom by

1 or 2 substituents independently selected from (1-4C)alkyl, amino, (1-4C)alkylamino, (1-4C)alkoxy and halogen, and/or on an available nitrogen atom (provided that the ring is not thereby quaternised) by (1-4C)alkyl; or

R^9 is a C-linked 6-membered heteroaryl ring containing 1 or 2 nitrogen heteroatoms, which ring is optionally substituted on any available C atom (provided that when the N atom is adjacent to the link, there is no substitution on any C atom that is adjacent to this N atom) by 1, 2 or 3 substituents independently selected from (1-4C)alkyl, amino, (1-4C)alkylamino, (1-4C)alkoxy, (1-4C)alkoxycarbonyl and halogen;

R^{10} is a C-linked 5-membered heteroaryl ring containing 2 to 4 heteroatoms independently selected from N, O and S, which ring is optionally substituted on an available carbon atom by 1 or 2 substituents independently selected from (1-4C)alkyl, amino, (1-4C)alkylamino, (1-4C)alkoxy, (1-4C)alkoxycarbonyl and halogen, and/or on an available nitrogen atom (provided that the ring is not thereby quaternised) by (1-4C)alkyl;

or

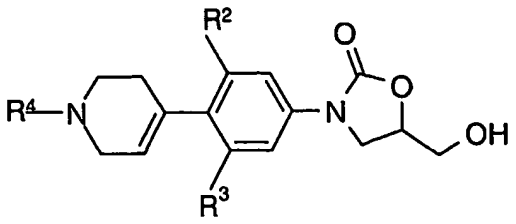
R^{10} is a C-linked 6-membered heteroaryl ring containing 2 or 3 nitrogen heteroatoms, which ring is optionally substituted on any available C atom by 1, 2 or 3 substituents independently selected from (1-4C)alkyl, amino, (1-4C)alkylamino, (1-4C)alkoxy, (1-4C)alkoxycarbonyl and halogen;

R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 5-membered heteroaryl ring, containing either (i) 1 to 3 further nitrogen heteroatoms or (ii) a further heteroatom selected from O and S together with an optional further nitrogen heteroatom; which ring is optionally substituted on a C atom by an oxo or thioxo group; and/or the ring is optionally substituted on a C atom by 1 or 2 (1-4C)alkyl groups; and/or on an available nitrogen atom (provided that the ring is not thereby quaternised) by (1-4C)alkyl; or

R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 6-membered heteroaryl ring containing up to three nitrogen heteroatoms in total (including the linking heteroatom), which ring is substituted on a suitable C atom by oxo or thioxo and optionally substituted on any available C atom by 1 or 2 (1-4C)alkyl substituents;R^2 and R^3 are independently hydrogen or fluoro;

which process comprises adding to a reaction vessel containing an activating agent

(i) an alcohol of formula (III)



(III)

where R^2 and R^3 are as defined above, and R^4 is hydrogen or a protecting group such as benzyl,

(ii) a compound of formula (IV)

XR^8

(IV)

where R^8 is as defined above, and

(iii) a trisubstituted phosphine or phosphite,

and thereafter, if necessary or desired carrying out one or more of the following steps:

a) removing any protecting group R^4;

b) recrystallising the product from water or a mixture of water in admixture with another solvent .

7. A process according to claim 6 wherein reagents (i), (ii) and (iii) above are premixed and added together to a solution of the activating agent.

8. A process according to claim 6 or claim 7 wherein the activating agent is diisopropylazodicarboxylate (DIAD).

9. A process according to any one of claims 6 to 8 wherein R^8 is a group OR^9.

10. A process according to claim 9 wherein R^9 is an isoxazole group.

11. A process according to claim 10 wherein R^9 is an isoxazol-3-yl.

12. A process according to any one of claims 6 to 11 where R^2 and R^3 are fluorine.

13. A process according to any one of claims 6 to 12 where R^4 is a protecting group such as benzyl.

14. A process according to any one of the preceding claims wherein the amount of activating agent used in the process is greater than the stoichiometric amount required.

15. A process according to claim 14 wherein at least 1.4 equivalents of activating agent is used for every one equivalent of the alcohol.

16. A process according to any one of the preceding claims wherein an excess of trisubstituted phosphine or phosphite is included in the reaction mixture.

17. A process according to claim 16 wherein the trisubstituted phosphine or phosphite is triphenylphosphine and at least 1.55equivalents of triphenylphosphine to the amount of alcohol is used.

18. A hydrate of a compound of formula (II) as defined in claim 6.

19. A hydrate according to claim 18, wherein the water of hydration content is between approximately 1% and approximately 5% w/w.

20. A hydrate according to claim 19 wherein the water of hydration content is 4% w/w.

21. A hydrate as claimed in claim 18, claim 19 or claim 20, wherein the compound of formula II is 5(R)-Isoxazol-3-yloxymethyl-3-(4-(1,2,5,6-tetrahydropyrid-4-yl-3,5-difluorophenyl)oxazolidin-2-one.

22. A process for purifying a compound of formula (II) as defined in claim 1, said method comprising dissolving the compound in water or water in admixture with a further solvent, and allowing the hydrate salt to crystallise therefrom.